IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re PATENT APPLICATION of
Michihiro Ohno et al.
Serial No. 10/537,325
Filed: June 2, 2005
For: BENZOMORPHOLINE DERIVATIVES

Atty. Docket No.: HIR-05-1144
Art Unit: 1624
Examiner: HABTE, KAHSAY

DECLARATION PURSUANT TO 37 C.F.R. 1.132

1. I, Michihiro Ohno, do hereby declare as follows:

I majored in medicinal chemistry and organic chemistry in University of Tokyo and received master's degree (in 1991) and Ph.D. pharmaceutical sciences (in 1994) from University of Tokyo.

In 1994, I entered employment with Toray Industries, Inc., and since then have been a researcher in the Pharmaceutical Research Laboratories. I have been engaged in research and development of the medicine using organic chemistry and medicinal chemistry in circulation and inflammation area. I engaged in the research of nucleoside and nucleotide receptors as post-doctoral researcher in National Institutes of Health (Bethesda, MD, USA) (2002-2004). Now, I am a chemistry team leader of the new anti-inflammatory agent research group.

I have a full knowledge of the present invention and cited references.

2. In order to demonstrate the patentability of the present invention, the following experiment was carried out.

Human platelet aggregation inhibitory test:

Blood collected from human median cubital vein was centrifuged at 800 rpm for 10 minutes. Upper portion of the resultant was collected as platelet rich plasma (PRP). PRP was dispensed to small test tubes, and 5 μM of ADP was added thereto to induce platelet aggregation. The degree of platelet aggregation was measured as a change in turbidity using an aggregometer (Hematracer 1, Nikobioscience). Each compound was added 1 minute before ADP addition, and calculation was carried out using as an IC_{50} value a concentration that inhibits aggregation by 50%.

The results of evaluating the activities of the compounds of the present invention by the methods are summarized in the following Table. As a result, the benzomorpholine derivatives of the present invention were revealed to have a stronger inhibitory effect of platelet aggregation compared with that of the compounds used in Examples 21 and 32 in U.S. Patent No. 6,407,096.

In Table 34 of the present Specification, Example 1-31 has two IC_{50} values of 31nM and 14nM, in which the IC_{50} value of 31nM is wrong. Thus, Example 1-31 has only the IC_{50} value of 14nM in the following Table.

Table

Example No. of Compound	Platelet Aggregation Inhibitory Effect IC_{50} (nM)
1-1	71
1-2	49
1-4	72
1-8	56
1-9	51
1-13	15
1-14	13
1-16	5.3
1-19	59
1-27	69
1-28	5.9
1-29	55
1-30	12
1-31	14
1-40	14
1-49	18
1-63	8.8
1-64	9.0
1-65	42
1-66	33
1-67	5.1
1-68	28
1-69	88
2-1	37
2-4	27
2-6	40
2-7	59
2-12	67
2-15	63
2-16	79
2-27	55
Patent Document * Compound of Example 21	1,800
Patent Document * Compound of Example 32	> 100,000

* U.S. Patent No. 6,407,096

3. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date: This 11 day of July, 2006

Michihiro Ohno

Michihiro Ohno